REMARKS

In view of the above amendments and the following remarks, the Examiner is respectfully requested to withdraw the rejections, and allow claims 1, 8, 14-16, 21, 24-26 and 32-46, the currently pending claims. Claims 1 and 24 have been amended. No new matter is added.

Support for the amending language, "for selective cytolysis of a target cell" may be found in the specification on page 8, lines 19-23.

Claims 1, 8, 14-16, 21, 25, 26 and 32-46 have been rejected under 35 U.S.C. 103 as being unpatentable over either one of Henderson *et al.* (WO97/01358); Hallenbeck *et al.* (WO96/17053), Walther *et al.* (Mol. Biotechnol. 6:267-286); Dachs *et al.* (Nat. Med. 3:515-520); Dachs *et al.* (Oncol. Res. 9:313-325); Advani *et al.* (Semin. Oncol. 24:633-638), and Parr *et al.* (Nat. Med. 3:1145-1149). Applicants respectfully submit that the presently claimed invention is not made obvious by the combination of cited references.

The Examiner states that Applicants have described each reference, noted where each reference fails and that the Examiner agrees with Applicants summary of each of the separate references (page 5 of the 11/26/02 Office Action; Paper 28). However, the Examiner argues that the combination of references render the claims obvious. Applicants respectfully disagree. The claims have been amended to more clearly recite the invention which is directed to adenovirus vectors "for selective cytolysis of a target cell".

Neither Henderson (WO 97/01358) nor Hallenbeck (WO 96/17053) teach or render obvious replication-competent adenovirus vectors that function in selective lysis of target cells. The specification of the instant case characterizes the adenovirus vectors of the invention as "replication-competent" (page 6, line 2) and states that the invention provides methods of suppressing tumor cell growth comprising contacting a tumor cell with an adenoviral vector of the invention such that the adenoviral vector enters the tumor cell and exhibits selective cytotoxicity for the tumor cell (page 8, lines 19-23).

As previously discussed, Henderson (WO 97/01358) describes "replication defective or replication competent adenovirus vehicles" and states that "by providing for regulated transcription restricted to specific host cell targets, one can provide for adenoviruses that can be used as vehicles for introducing genetic capability into host target cells, as distinct from other host cell types. The transgenes serve to modify the genotype or phenotype of the target cell...". The application does not state that replication of the adenovirus results in selective cytotoxicity to the target cell.

Hallenbeck (WO 96/17053) states that "a general object of the invention is to provide novel vectors for tissue-specific vector replication and gene expression from the replicating vector" and "a further object of the invention is to selectively distribute a heterologous gene product in a target tissue." Essentially Hallenbeck has added a tissue specific element to an adenoviral viral vector making it replication-conditional. However, the viral vector is a gene delivery vehicle and the only mention of cellular cytotoxicity is due to an expressed cytotoxic gene (TK, CD, etc.).

Taken as a whole, both Henderson (WO 97/01358) and Hallenbeck (WO 96/17053) teach cell specific

delivery of transgenes, wherein the transgenes may cause cytotoxicty to the target cell. In contrast to the present invention, neither Hend rson nor Hallenbeck teach or suggest replication-competent adenovirus vectors for selective cytolysis of a target cell, wherein propagating of the adenovirus is cytotoxic to the cell.

On page 6 of the 11/26/02 Office Action; Paper 28, the Examiner makes this very point, wherein the Office Action states that the motivation for combining references is that at the time the invention was made it would have been prima facie obvious to combine the cell status-specific TREs of Walther *et al.*, Dachs *et al.*, Dachs *et al*, Advani *et al.* and Parr *et al.* with the conditionally-replication competent adenovirus vectors of Henderson and Hallenbeck because operable linkage to radiation-inducible, heat-inducible, hypoxia-inducible or cell cycle-inducible inducible regulatory elements "allows for more effective and selective transgene expression and tumor eradication with significantly less normal tissue toxicity than seen with standard adenoviral vectors"

The Walther *et al.*, Dachs *et al.*, Dachs *et al*, Advani *et al.* and Parr *et al.* references describe various cell status regulatory elements that are useful in gene delivery vehicles. This disclosure does not compensate for the lack of teaching in Henderson (WO 97/01358) and Hallenbeck (WO 96/17053) relative to replication-competent" adenoviral vectors that enters a target cell (i.e. a tumor cell) and exhibits selective cytotoxicity for that cell. The combined references do not provide a reasonable expectation of success in practicing the present invention. In contrast to Henderson and Hallenbeck, the adenoviral vectors of the present invention do not require the presence of a cytotoxic transgene, as further discussed above forth above.

In view of the above remarks, withdrawal of the rejection under 35 U.S.C. 103 is requested.

CONCLUSION

Applicants submit that all of the claims are now in condition for allowance, which action is requested.

The Commissioner is hereby authorized to charge any other fees under 37 C.F.R. §§ 1.16 and 1.17 which may be required by this paper, or to credit any overpayment, to Deposit Account No. 50-0815, order number CELL-014.

Respectfully submitted,

Date: _____, 2002

By: _____
Linda R. Judge
Registration No. 42,702

Linda R. Judge
Cell Genesys, Inc.
342 Lakeside Drive
Foster City, CA 94404
phone (650) 425-4650
fax (650) 349-7392

APPENDIX
VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. (amended) A replication-competent adenovirus vector for selective cytolysis of a target cell comprising,

a hypoxia responsive element (HRE) operably linked to an adenovirus gene essential for replication selected from the group consisting of E1A, E1B and E4, wherein said HRE comprises a binding site for hypoxia inducible factor-1.

24. (amended) A composition comprising:

a replication-competent adenovirus vector for selective cytolysis of a target cell comprising a hypoxia responsive element (HRE) operably linked to an adenovirus gene essential for replication selected from the group consisting of E1A, E1B and E4, wherein said HRE comprises a binding site for hypoxia inducible factor-1; and a pharmaceutically acceptable excipient.